WeS27 Relation between superantigen-induced inflammatory cytokines severity of invasive group A streptococcal infections

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Cytokines elicited by bacterial superantigens have been suggested to play a central role in severe systemic clinical manifestations of gram-positive sepsis. Analyses of *in vivo* and *in vitro* cytokine responses in patients with severe (streptococcal toxic shock syndrome and/or necrotizing fasciitis) or non-severe (no toxic shock or deep-tissue involvement) group A streptococcal invasive infection revealed a direct correlation between cytokine responses and severity of invasive group A streptococcal disease. Significantly elevated frequencies of pro-inflammatory cytokines were observed in acute phase peripheral blood mononuclear cells from severe cases as compared to non-severe cases. Similarly, in vivo inflammatory cytokine responses were markedly higher in tissue biopsies of patients with necrotizing fasciitis than in severe cellulitis/limited necrosis. Importantly, this difference in *in vivo* cytokine responses during acute phase could be reproduced when paired age and sex-matched severe and non-severe cases infected with a clonal streptococcal strain were tested *in vitro* during their convalescent phase for immune response to culture supernatants from their infecting isolate. Thus, our data indicate that inherent host factors determine the magnitude of cytokine responses to streptococcal superantigens, and consequently the clinical outcome of infection. The importance of host factors, specifically HLA class II, was further supported by in vitro experiments using cells transfected with previously identified risk- and protective HLA class II molecules, inasmuch as the risk HLA alleles promoted significantly stronger responses to streptococcal superantigen than did the protective alleles.

S29 – Antimicrobial resistance - evolution and . . .

WeS31 Role of mutator alleles in the generation of multi-resistant strains

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As WHO stated in one of its report, "every bacteria possess an inherent flexibility that enables them sooner or later to evolve antimicrobial resistance genes". To be able to take into account some of this flexibility, we have developed a multidisciplinary network including MDs, population geneticists, ecologists and molecular biologists. Among natural isolates of E. coli and Salmonella the mutation rates to antibiotic resistance are higly variable (LeClerc *et al.* 1996 Matic *et al.* 1997). Mutator alleles, such as mismatch repair deficiency, can enhance up to 1000-fold mutation and recombination rate (Vulic *et al.* 1997).

Modelling (Taddei *et al.* 1997b) and experimental evolution (Chao and Cox, 1983; Mao *et al.* 1997; Sniegowski *et al.* 1997) can show that such a high mutation rate can be favoured and speed up bacterial adaptation to new challenges (Taddei *et al.* 1997a) such as antibiotic treatment thus generating multiresistant strains.

WeS33 Evolution to ameliorate the biological costs of antibiotic resistance

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The frequency of antibiotic resistance in a bacterial population is, apart from the volume of antibiotic use, mainly determined by the fitness and transmission costs of resistance combined with the ability of the resistant bacteria to compensate for these costs by mutations. Most resistances decrease bacterial fitness as measured by competition experiments between sensitive and resistant strains in the absence of antibiotic. These costs can be reduced by compensatory mutations without any loss of resistance. Recent results show that the rate and nature of the compensatory mutations is strongly affected by the growth environment. Thus, streptomycin- and fusidic acid resistant *Salmonella typhimurium* that evolve in mice or laboratory medium obtain different compensatory mutations. These differences in mutation spectra are caused either by an environment-specific formation or selection of the compensated mutants. These results suggest that the evolution to ameliorate the costs of antibiotic resistance may follow different trajectories within and outside a bacterial host.

S30 – Vaccines in pregnancy and infancy

WeS36 BCG vaccination

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The Bacille Calmette-Guérin (BCG) vaccine, for the first time administered by WeillHallé to a newborn child exposed to an infectious parent in July 1921 with no adverse outcome found its application rapidly spreading within a few years. The initial indication was limited to newborn children exposed closely to a parent with infectious tuberculosis and shown to reduce fatality from childhood tuberculosis by some 80 per cent. Once safety of the vaccine was established, the indication was expanded to children in general, and the parenteral administration replaced the original oral vaccination without loss of efficacy. Today, BCG has cumulatively been given to more children than any other vaccine, yet its value in the control of tuberculosis remains circumspect. The vaccine has undergone several genetic mutations and various strains of BCG exist today, and the protection it affords varies greatly in different situations. The 15-year follow-up results of the largest every conducted trial, in Chingleput, South India, have just been published and shown no protection against bacteriologically confirmed tuberculosis. On the other extreme, BCG continues to provide, e.g., high protection in British school children. A variety of hypotheses have been offered to provide possible explanations for this variation in protective efficacy, yet none is fully satisfactory. What is rather consistent, however, is the original notion that BCG vaccination provides considerable protection against a fatal outcome from serious forms of childhood tuberculosis. Its impact on the epidemiological situation of tuberculosis is, on the other hand, generally accepted to be minimal. Policy decisions on the use of BCG must thus take into account the frequency of serious, not otherwise preventable forms of tuberculosis in children versus the frequency of adverse reactions (albeit infrequent), and the desirability to preserve the usefulness of the tuberculin skin test in contact investigations, as well as cost-effectiveness of its continued use. The variation in protective efficacy in different areas of the world would ideally require an assessment of its value through case-control studies in each setting faced with a decision on the continuation or abolition of its use in routine practice, coupled with an analysis of its cost-effectiveness.

WeS37 Conjugate vaccines allow earlier administration of polysaccharide vaccines

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Many pathogenic bacteria, including *N. meningitidis*, *S. pneumoniae*, type B *H. influenzae*, produce a polysaccharide capsule that is made by many repeating units of a simple sequence of one or more sugars. Vaccines containing purified, high molecular weight polysaccharides induce protective immunity in adults. They were introduced in the 70s and are available against meningococcus and pneumococcus. These vaccines induce a T-cell-independent immunity, because polysaccharides are unable to bind the T-cell receptor and therefore stimulate only B cells. T-cell-independent vaccines induce an IgM-mediated antibody response that cannot be boosted by subsequent immunizations and is effective only after two years of age. In infants polysaccharide vaccines usually do not work at all. To overcome the limit of the T-cell independence of this type of vaccines, bacterial polysaccharides or oligosaccharides containing many repeating units have been chemically coupled to T-cell-dependent protein antigens. The resulting semisynthetic conjugate vaccines are T-cell-dependent and induce an IgG-based immune response and memory, so that it can be boosted by subsequent infection and immunization. Moreover, the conjugate vaccines have the great advantage of working in infants below two years of age. The development of conjugate vaccines allowed the introduction of mass vaccination of infants against *H. influenzae*, that has been one of the most successful vaccinations introduced during the last decade. In five years this vaccination has virtually eliminated infant meningitis caused by *H. influenzae* in the USA and all countries where vaccination has been introduced. Clinical trials are presently ongoing with conjugate vaccines against meningococcus A and C and against the most common serotypes of pneumococcus. These vaccines will be introduced within a few years and are expected to eradicate most causes of bacterial meningitis. A polysaccharide vaccine based